REMARKS/ARGUMENTS

In response to the Office Action of May 24, 2006, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1 and 39 been amended. Claims 2-38 were cancelled in a previous response (filed on August 21, 2003). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer marker of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is currently under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the specification made herein.

The paragraph at page 24 has been amended to correct a

typographical error (luymph to lymph).

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to clearly indicate that the ~~c~~laimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) evidences a link to Alzheimer's disease. This language is supported by the specification as originally filed, for example at page 35, lines 14-18.

The Examiner notes that at page 20 of the Response, Applicant refers to supposed amendment of the claim to indicate that "the isolated peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 is linked to Alzheimer's disease", but there appears to be no such recitation within the text of the claim.

Applicants note that at page 20 of the Response filed on June 27, 2005, Applicants indicate that the claims have been amended to note that the claimed peptide is linked to Alzheimer's disease, see claim 39. The phrase "evidencing a link to Alzheimer's disease" is recited in claim 1 as presented herein.

Claim 39 has been amended to clarify the steps of the recited method.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of an

isolated biopolymer marker consisting of amino acid residues 2-18 of SEQ ID NO:1, a search of these claims would encompass this specific biopolymer marker. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected inventions, under the decision in *In re Ochiai* (MPEP 2116.01) with claims (claim 1) of the elected invention, upon the Examiner's determination that the claim of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker consisting of amino acid residues 2-18 of SEQ ID NO:1 is found to be novel, methods and kits limited to its use should also be found novel.

Rejection under 35 USC 101

Claim 1, as presented on June 27, 2005, stands rejected under 35 USC 101 because the claimed invention allegedly is not supported by either a specific, substantial and credible asserted utility or a well established utility essentially for reasons of record with respect to the 35 USC 112, first paragraph, lack of enablement rejection in previous office actions of record.

The Examiner asserts that claim 1, as currently amended, is directed to a biopolymer marker consisting of amino acid sequence 2-18 of SEQ ID NO:1. It is noted at page 20 of the Response that Applicant refers to supposed amendment of the claim to indicate that "the isolated peptide consisting of amino acid residues 2-18 of SEQ ID NO:1 is linked to Alzheimer's disease". However, there appears to be no such amendment of record presented within the text of claim 1.

Further, it is important to point out that throughout the text of the Response filed on June 27, 2005, Applicant submits that the instant claimed peptide 2-18 of SEQ ID NO:1 is not diagnostic for Alzheimer's disease (AD) or any other pathological condition but is linked to AD (middle at page 21, pp. 28-29, especially top at page 30). The instant specification presents several definitions of a "biopolymer marker" (see pages 5, 6 especially 11 and 21), essentially that it is a polymer of biological origin (bottom at page 21), which can be present/absent/down-regulated/up-regulated with respect to a disease condition (page 11). However, according to Webster's dictionary "a marker" is "one that marks or distinguishes". The instant invention is based on the assertion that a peptide fragment 2-18 of SEQ ID NO:1 is differentially expressed in patients suspected of having AD from control normal individuals. The Examiner asserts that there appears to be no

further information presented in the instant specification as to what constitutes the finding of a peptide 2-18 of SEQ ID NO:1 in a sample. For example, if a peptide 2-18 of SEQ ID NO:1 was found in a sample obtained from a patient, what would that mean to the skilled practitioner? Does it mean that a patient has AD, or is at risk of developing the disease? The Examiner asserts that the instant specification fails to provide any factual evidence that finding of a peptide 2-18 of SEQ ID NO:1 could lead to any meaningful determination for diagnosis or treatment of Alzheimer's disease, as asserted by Applicant. Thus, in order to practice the claimed invention, a skilled artisan would have to engage in a substantial amount of further research to establish what constitutes "link to Alzheimer's disease" and, eventually, establish the utility of the claimed peptide 2-18 of SEQ ID NO:1 in the diagnostics of Alzheimer's disease.

At pp. 21-28 of the Response, Applicant traverses the instant rejection on the premises that the specific and substantial credible utility of the claimed biopolymer marker as being linked to Alzheimer's disease (AD) is based on the showing "that the biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) is present in samples of body fluid obtained from Alzheimer's patients, but is not present in samples of body fluid obtained from patients who were age matched with the Alzheimer's patients

(controls)" (pp. 21-22). The Examiner concludes that Applicants' arguments have been fully considered but are not persuasive.

The instant specification provides a disclosure of a protocol, under which samples of blood collected from AD patients, age-matched controls and pooled control samples were analyzed by using mass spectrometric and chromatographic techniques. The results of the analysis are presented in Figure 1 and also within the text of the instant specification. Specifically, finding of the "disease specific marker" identified by an amino acid sequence is presented at page 46 of the instant specification. Figure 1 is described as "photograph of a gel which is indicative of the presence/absence of the marker in disease vs. control and, in cases where the marker is always present, the relative strength, e.g, the up or down regulation of the marker relative to categorization of disease state is deduced" (p.46). Brief Description of the Figure (page 37) does not contain any disclosure of how fragment 2-18 of SEQ ID NO:1 corresponds to the bands as shown in Figure 1. The text on pp. 45-46 is limited to the description of finding of three peptides (2-18 of SEQ ID NO:1 among them) "related to Alzheimer's disease" and reference to Band 2. Without any further information being present in the instant specification, as filed, which includes analysis of Figure 1 and Band 2 being present only in one AD sample, it is not clear how a skilled practitioner can use the instant disclosure and

peptide 2-18 of SEQ ID NO:1 for diagnostic or clinical purposes, as currently asserted. The Examiner maintains that based on the information presented in the instant specification as originally filed, the instant claimed invention, an isolated biomarker 2-18 of SEQ ID NO:1, asserted to be useful for diagnostics and therapeutics of Alzheimer's disease, clearly lacks specific and substantial credible real-world utility and, therefore, the instant invention does not meet the requirements of 35 USC 101.

At pp. 23-32 of the Response, Applicant refers to several publications to explain as how differentially expressed proteins are used as disease markers. The Examiner fully agrees that identification and selection of reliable biomarkers to diagnose pathological conditions is a known practice. Moreover, identification of a marker that is specifically associated with a particular condition (present/absent or present at specific altered levels as compared to normal control) constitutes a specific and substantial credible utility even if a biological role of the molecule itself is not known or disclosed. However, the Examiner asserts that this is not the factual situation in the instant case. In the instant case, Applicants' invention is predicated on the finding that samples of blood taken from patients suspected of having AD contain proteins in the forms and amounts that are different from normal control samples. Applicant further

extrapolates this result into a diagnostic tool for AD. Accordingly, it would appear that Applicant provides a single finding (the finding), and then presents an invitation to experiment to determine the level of differential expression of peptide 2-18 of SEQ ID NO:1 that is diagnostic of AD, and then to assay if the peptide could be used to diagnose AD, such as to distinguish AD from normal state and from other similar neurodegenerative conditions, as well as to treat AD.

The Examiner explains that the US Court of Appeals for the Federal Circuit recently addressed the utility requirement in the context of a claim to DNA. See *In re Fisher*, 2005 WL 2139421 (Sept. 7, 2005). The *Fisher* court interpreted *Brenner v. Manson*, 383 US 519, 148 USPQ 689 (1966), as rejecting a "de minimis view of utility" 2005 WL 2139421, at *4. The *Fisher* court held that 101 requires a utility that is both substantial and specific. *Id.* at *5. The court held that disclosing a substantial utility means "show[ing] that an invention is useful to the public as disclosed in its current form, not that it may be useful at some future date after further research. Simply put, to satisfy the "substantial" utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public." *Id.*

Just as in the *Fisher* case where the Board reasoned that use

of the claimed ESTs for the identification of polymorphisms is not a specific and substantial utility because "[w]ithout knowing any further information in regard to the gene represented by an EST, as here, detection of the presence or absence of a polymorphism provides the barest information in regard to genetic heritage" (Id., slip op. at 15), in the instant case, detection of peptide 2-18 of SEQ ID NO:1 in a sample of a patient suspected of having Alzheimer's disease provides no meaningful information as to the diagnosis determination. While an assay that detects the presence of a marker that has a stated correlation to a specific disease condition would be considered a "substantial utility" in the context of providing a diagnostic tool, in the instant case the claimed peptide is suitable only for further research, which constitutes a utility that is not considered a "substantial utility". See *Brenner v. Manson*, 148 USPQ 689 (Sus. Ct. 1966), in which the court expressed the opinion that all chemical compounds are "useful" as it appears in 35 USC 101, which requires that an invention must have either an immediate obvious or fully disclosed "real world" utility.

Finally, the Examiner asserts with respect to Applicants' statement that the claimed biopolymer marker is not "a unique marker for any particular disease or condition" evidence a link to Alzheimer's disease (top at page 30), the Examiner maintains that

disclosure of a peptide fragment 2-18 of SEQ ID NO:1 as being linked to a pathological condition constitutes a utility, which requires further research to identify or reasonably confirm a "real world" context of use. At present, it appears that the only information obtained from identifying the presence of a biopolymer marker 2-18 of SEQ ID NO:1 is the determination of "a link to AD". One skilled in the art readily appreciates that many factors have a link to or are associated with a particular pathological condition. In *Brenner v. Manson*, 148 USPQ 689 (Sus. Ct. 1966), the court specifically stated that "a patent is not a hunting license". [i]t is not a reward for the search, but compensation for its successful conclusion". To grant Applicant a patent encompassing isolated fragments of a naturally occurring human protein, which are not readily useable in their current form, would be to grant Applicant a monopoly "the metes and bounds" of which "are not capable of precise delineation". That monopoly "may engross a vast, unknown, and perhaps unknowable area" and "confer power to block off whole areas of scientific development, without compensating benefit to the public" *Brenner v. Manson, Ibid.* To grant Applicant a patent on the claimed peptides based solely upon an assertion that the protein is linked to Alzheimer's disease is clearly prohibited by this judicial precedent since the compensation to the public is not commensurate with the monopoly granted.

Thus, since the instant specification does not disclose a credible "real world" use for the isolated biopolymer marker 2-18 of SEQ ID NO:1 in currently available form, then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 USC 101 as being useful.

Applicants respectfully disagree with the Examiner's conclusion and assert that the claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) has both a specific, substantial and credible utility and a well-established utility.

It is well known that pathological changes in an organism can be reflected by changes in the serum protein pattern. A diagnosis may be predicted based upon the similarity of an unknown sample pattern to a known sample pattern. Serum protein patterns are established by mass spectrometry.

Proteins, as collected from a serum sample, are too large to be effectively resolved by mass spectrometry and thus, are first subjected to separation by polyacrylamide gel electrophoresis. The resulting protein bands in the polyacrylamide gel which are deemed to be different between two comparable states are excised from the gel and subjected to further fragmentation by enzymes. These resulting peptides are then collected and purified by chromatography prior to identification using mass spectrometry. The peptides undergo step-wise degradation into sequence-defining

fragments, i.e. the peptides are part of the original protein found in the serum sample. The resulting mass spectral profile is composed of parts of the original protein. See page 37, line 19 to page 40, line 2 of the instant specification.

In order for a rejection under 35 USC 101 to be appropriate the Examiner must demonstrate that there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention (*In re Joyce A. Cortright* 49 USPQ 2d 1464 1999).

It is respectfully submitted that the "link to Alzheimer's disease" asserted by Applicants, was elucidated under real-world conditions according to a methodology as set forth in the following steps:

I) isolating peptides from body fluid samples obtained from two groups of patients,

a) one group known to suffer from Alzheimer's disease; and b) a group of healthy controls age-matched with the Alzheimer's group;

II) carrying out the protocols disclosed in the specification (see pages 37-47);

III) comparing the expression pattern of protein bands from the two groups of patients as evidenced in gels (such as that shown in Figure 1);

IV) subjecting the observed expression pattern to the criteria as disclosed at page 11, lines 9-20 of the instant specification;

V) excising bands that are differentially expressed between the two groups, and, submitting the peptides present within the excised bands for sequence identification by mass spectrometry. In the instant case, Band #2, as shown in Figure 1, was excised from the gel as it was present in samples obtained from patients having Alzheimer's disease and absent in samples obtained from age-matched control patients. Upon mass spectrometric analysis, three differentially expressed peptides, including the claimed peptide (amino acid residues 2-18 of SEQ ID NO:1) were identified from Band #2.

The instant inventors, using the above described methodology in a real-world environment, thereby elucidated and identified amino acid residues 2-18 of SEQ ID NO:1 as a fragment of plasma protease C1 inhibitor precursor proteins found in Alzheimer's patients but absent in age-matched, healthy control patients, thus establishing the instantly claimed link to Alzheimer's disease evidenced by the observed differential expression. Thus, the claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) can be used as a marker for Alzheimer's disease as it can distinguish between Alzheimer's disease patients and age-matched healthy patients.

Furthermore, in the Response filed on June 27, 2005, Applicants provided articles that evidence identification of disease markers by their observed differential expression is a common and an acceptable practice (Patterson and Gunnerson et al., at pages 23 and 30 of the Response, respectively).

The mass spectral profile indicative of this marker was disclosed in the Declaration under 37 CFR 1.132 filed on August 21, 2003. Mass spectral profiles are reproducible, and are typically published for reference purposes.

Thus, any skilled artisan, in a real-world context, and without significant further research, could utilize the mass spectral profile provided as a reference for comparing with mass spectral profiles of peptides obtained from an unknown sample to test the unknown sample for a link to Alzheimer's disease, thereby establishing a disclosed specific and substantial credible utility for the instantly claimed peptide.

Although the Examiner does not dispute the fact that the claimed peptide is found in Alzheimer's disease, the Examiner does not find its use as a marker linked to Alzheimer's disease to be credible.

As evidenced by the discussion above, the instant specification clearly provides data (Figure 1) which sets forth the use of the claimed peptide (amino acid residues 2-18 of SEQ ID

NO:1) as a marker linked to Alzheimer's disease.

Furthermore, as set forth in *Raytheon Company v. Roper Corporation* (220 USPQ 592 1983), if an invention meets at least one stated utility, utility as a whole is established. The instant invention clearly meets the objective, stated in the specification as originally filed at page 35, lines 14-18, of evaluating samples containing a plurality of biopolymers for the presence of a biopolymer marker which evidences a link to at least one specific disease state.

Additionally, in contrast to the holding in *Fisher* (*In re Fisher* 76 USPQ 2d 1225 2005), where ESTs were deemed not to have a substantial and credible utility, the instantly claimed peptide does indeed evidence a specific use as a marker for Alzheimer's disease supported by data specifically directed to patients having Alzheimer's disease.

Furthermore, the instant invention meets the *Fisher* test of disclosure of a substantial utility by showing that an invention is useful to the public as disclosed in its current form, not that it may be useful at some future date after further research, and thus a significant and presently available benefit to the public is disclosed.

With regard to the credibility of Applicants' showing, precedent dictates that a holding of lack of credibility by an

Examiner can only be made if the Examiner has reason to doubt the objective truth of the statements contained in the written description (*In re Joyce A. Cortright* 49 USPQ 2d 1464 1999). In the instant situation, the Examiner does not appear to doubt Applicants' statements and acknowledges the presence of Band #2 in Alzheimer's disease (page 5 of the Office Action mailed on May 24, 2006) and further recognizes that identification of a marker that is specifically associated with a disease condition by its differential expression constitutes a specific and substantial credible utility even if a biological role of the molecule itself is not known or disclosed (page 6 of the Office Action mailed on May 24, 2006).

In view of these statements, and further in conjunction with the fact that the Examiner has failed to present any countervailing facts and reasoning sufficient to establish that a person of ordinary skill in the art would not believe the Applicants' assertion of utility (*In re Brana* 34 USPQ 2d 1436 1995), it is respectfully submitted that credible utility has been established.

In light of the foregoing remarks, Applicants respectfully submit that the Examiner has failed to meet the burden of establishing a *prima facie* case for lack of substantial and credible utility.

In conclusion, based upon all of the above arguments,

Applicants respectfully submit that one of ordinary skill in the art would immediately appreciate why Applicants regard the claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) as useful.

Accordingly, Applicants assert that the claimed invention has both a specific and a well-established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on June 27, 2005, stands rejected under 35 USC 112, first paragraph. Specifically, the Examiner asserts that since the claimed invention is not supported by either a clear asserted utility or a well established utility, one skilled in the art would clearly not know how to use the claimed invention.

Applicants respectfully disagree with the Examiner's assertions.

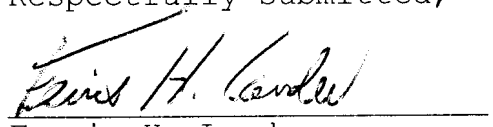
It has been established by prior arguments in the instant response that the claimed invention has both a clear asserted utility and a well established utility. Applicants assert that one of skill in the art would know how to use the claimed biopolymer marker (amino acid residues 2-18 of SEQ ID NO:1) as a marker for Alzheimer's disease. Therefore, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be

withdrawn as it was a consequence of the finding of a lack of utility which has now been rebutted.

CONCLUSION

In light of the foregoing remarks, amendment to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



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